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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/651,668 | 08/28/2003 | Alexei Brooun | SYR-ISPA-5001-C1 | 9129 |

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| EXAMINER | |
|---|---|
| KIM, ALEXANDER D | |
| ART UNIT | PAPER NUMBER |
| 1656 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/05/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/651,668 | BROOUN ET AL. | |
| | Examiner | Art Unit | |
| | Alexander D. Kim | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1, 4, 6, 9, 10, 16 and 18-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6, 9, 10, 16, and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 July 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Application Status*

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/06/2007 has been entered.

Applicants amendment canceling Claims 2-3, 5, 7-8, 11-15, and 17; amending Claims 1, 6, 10, 16, and 19-20 in the paper of 9/6/2006 is acknowledged. Thus, Claims 1, 4, 6, 9, 10, 16, and 18-23 are pending in the instant Office action.

### *Priority*

2. As previously noted, the application claims no priority for benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c).

### *Withdrawn-Objections to the Specification*

3. The previous objection of an Abstract for not completely describing the disclosed subject matter (see M.P.E.P. § 08.01(b)) is withdrawn by the virtue of Applicants' the amendment, received on July 5, 2006.

### *Objections to the Specification*

The specification is objected to because of the following informalities:

4. The specification is objected because inappropriate use of SEQ ID NOs and number of residues that do not corresponds to the SEQ ID NOs. For example, in §00180, the specification recites a "residues 544-935 (from SEQ. ID No. 1)" which is unclear because the SEQ ID NO: 1 is only 314 amino acid long. Also, the specification recites "which corresponds to the catalytic domain of human IspA" for SEQ ID NO: 1 is unclear because the SEQ ID NO: 1 is an E. coli protein according to the sequence listing. The recitation of "Thr and Ser residues at positions 182-183, respectively, (SEQ. ID No. 2)" is unclear because the SEQ ID NO: 2 is a nucleotide and there are no Thr and Ser in the corresponding position in SEQ ID NO: 1. Clarification is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification, especially the sequence residues and SEQ ID NOs.

5. According to the instant Example 2, an "IspA protein samples (corresponding to SEQ ID NO: 1)" were used in crystallization. However, the Example 1 disclose making two different protein, i.e., (a) "the full-length IspA with non-cleavable amino-terminal six histidine tag ---, in Figure 1 (residues 1-15 of SEQ ID No. 1)", which implies the protein used in crystallization is the entire SEQ ID NO: 1. On the other hand, (b) "the recombinant IspA catalytic domain with a 6x-histidine tag at the N-terminus followed by a rTEV protease cleavage sequence to facilitate tag removal (the excised 6x-Histidine

tag and rTev cleavage site sequences are underlined in SEQ ID No. 2)" (see page 48, top). However, there is no cleavage site in the protein of SEQ ID NO: 1 encoded by the nucleotide of SEQ ID NO: 2. It is unclear which protein is used in the actual crystal. Clarification is required

6. The specification is objected because of potential typographical error in the Oath and Declaration. The inventor Alexei Brooun in the instant Oath and Declaration may be Alexei Broun (with one "o") according to the publication of Hosfield et al. (2004, The Journal of Biological Chemistry, vol. 279, pages 8526-8529; as cited in the previous Office Action, 3/31/2006).

***Objections to the Drawing***

7. The drawings are objected to because the corrected drawing filed on 07/05/2006 is missing pages at the end compared to the original Figure 3. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement

sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 4, and 16 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 (Claims 1 and 4 dependent therefrom) recite the limitation "a protein in crystalline form". It is unclear if the claim is limited to a crystallized protein or any form of said protein comprising amino acids which is placed in a three-dimensional structure shown by the crystallized protein. The protein in solution or in a form of precipitation would have same three-dimensional structure as the three-dimensional structure in the crystallized protein at a particular time. Clarification is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4, 6, 9, 10, 16, and 18-23 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims 16 and 19 (Claims 1, and 4 dependent therefrom) are drawn to a protein crystal and methods of making a crystal having a certain unit cell dimensions and residues 1-314 (or 14-314 because of unclear instant disclosure of specification as described above) of SEQ. ID NO: 1 with optional additional limitations presented in individual, dependent claim form such as: a certain resolution (Claims 4 and 9), or a space group $P4_122$. It is noted that the composition of Claim 19 reads on a crystal comprising a protein of SEQ ID NO: 1. While the structure and function of one species of said genera of IspA are disclosed in the specification, the common structural characteristics of species that define said genera are not described.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons and reasons described in earlier Office Actions. Applicants argue "the application meets the written description requirement because the application is sufficient to show that the inventor possessed the claimed genus invention

(see bottom of page 4 and middle of page 5 in Remarks received on 02/06/2007), wherein the genus is the proteins in any crystalline form. Applicants argue "crystal by itself is a distinguishable structure feature" and "the space group and unit cell dimensions are not necessary to describe a protein in crystalline form." (see top of Remarks, page 5). However, as described in earlier Office Actions and below, "a singular chemical can crystallize differently based on the crystallization conditions" (see description below and Non-Final Office Action on 03/31/2006) and the instant crystallization condition(s) disclosed in the instant Example cannot predict the crystallization condition(s) for all crystal encompassed by the claimed genus; having any space group, any unit cell dimension, any space group and with or without any ligand(s). Applicants also argue the inventors picked one crystal out of numerous crystals prepared by the series of crystallization conditions as shown in Table 8, page 20 (see Remarks, top of page 6). The instant Table 8 may describe the structure of crystallization condition but lacks the function of forming a genus crystal encompassed by the claims; thus, there are no correlation between the structure and function of the genus to predict formation of any crystalline form. Also, instant specification discloses only one crystal as shown in Table 9, page 24 with X-ray diffraction quality. Applicants also acknowledge "Over 1000 individual trials were performed in which pH, temperature and precipitants were varied" and further require "Fine screening --- for those crystallization conditions that appeared to produce precipitate and/or crystal in the drops" (see Remarks, page 5, lines 18-24) to make the instant crystal only in the

presence of ligands (emphasis added, for example, IPP+Risedronate, see specification page 49).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

Although, Example 2 describes the crystallization of *E. coli* IspA [residues 1-314 (or 14-314 because of unclear instant disclosure of specification as described above) of SEQ ID NO: 1] in the presence of ligands disclosed on page 49 of instant specification, the specification describes one species of an IspA crystal with isopentylpyrophosphate (IPP) that falls within the instant genera of crystal. The crystal form described by Figure

2-6 is within the genera of Claims1, 4, 6, 9-10, 16, and 18-23 based on their sequence, space group symmetry, unit cell dimensions (including error), and resolution.

While the claim language requires a function for the instant genera of crystals (that of IspA), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately structurally described, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. The species noted above has adequately met this burden by the description in the instant specification. However, the composition of the crystals encompassed by the breadth of the claims is not described because the exact molecule(s) is not limited nor the space group and unit cell dimensions associated with this breadth of chemical composition described. In Claims 1 and 4, the composition of the crystal is not adequately described. The exact polypeptide sequence (SEQ ID No. 1), even with ligands in Claims, accompanied by the word "comprises" does not disclose the exact composition of the protein crystal in Claims 1 and 4. The SEQ ID NO: 1, space group, and unit cell dimensions disclosed in Claims 1 and 4 satisfies a part of adequate description but missing the ligand used in co-crystallization. A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-

ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350, provided in previous Office Action). One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the disclosed species of the instant disclosure. Therefore, claims drawn to the instant genera of crystals are also not adequately described. Thus, a skilled artisan would recognize that applicant was in possession of the claimed invention.

Claim 6 (Claims 9-10, and 18, 20-23 dependent therefrom) are further rejected under 35 U.S.C. 112, first paragraph, written description, as failing to comply with the written description requirement. Because the instant claims are drawn to methods of making and using a composition comprising a protein crystal consists of residues 1-314 (or 14-314 because of unclear instant disclosure of specification as described above) of SEQ ID NO: 1 under a suitable conditions for forming a protein crystal.

Although, Example 2 describes a method of crystallizing *E. coli* IspA [residues 1-314 (or 16-314, unclear according to the instant specification) of SEQ ID NO: 1] in the presence of ligands in seven different combinations, the specification disclose a description of only one species of an IspA crystallization that falls within the instant genera of crystallization that is within the genera of Claims 6, 9-10, and 18-23 based on their protein crystal composition, space group symmetry, unit cell dimensions (including error), and resolution. A genus method of making a protein crystal with any ligand in Claims cannot be adequately described by the species of crystallizing *E. coli* IspA in the

presence of IPP disclosed by the instant specification. The species of instant case does not correlate structure and function from species to genus method.

Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, a method of the crystallization encompassed by the breadth of the claims is not adequately described by the method of crystallization disclosed in the specification. In general, for a species of method of crystallization to be adequately structurally described, the following must be adequately disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably a SEQ ID NO of all included residues) (2) any ligand added (emphasis added) (3) the precipitant solution. The species of method of crystallization noted in Example 2 of the instant specification have adequately met this burden. However, a very broad and widely variable crystallization method encompassed by the breadth of the claims is not described. A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350, provided in the previous Office Action). Therefore, the crystallization condition disclosed in the specification to crystallize 1-314 of SEQ ID NO: 1 cannot sufficiently describe any

suitable condition encompassed by the instant genus Claims. Thus, a skilled artisan would recognize that applicant was in possession of the claimed invention.

10. Claims 1, 4, 6, 9-10, 16, and 18-23 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method for preparing a co-crystal of a polypeptide consisting of residues 1-314 (or 14-314 because of unclear instant disclosure of specification as described above) SEQ ID NO: 1 by a method of crystallizing a ternary complex consisting of said polypeptide with ligands (IPP+Risedronate, see specification page 49), that results in a crystal having the space group $P4_122$ and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90°$, does not reasonably provide enablement for all crystals and methods comprising the steps of using any suitable condition for the preparation of the co-crystal as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. It is noted that the composition of Claim 19 reads on a crystal comprising a protein of SEQ ID NO: 1.

Applicants argue "a considerable amount of experimentation is permissible, if it is merely routine" and the specification "provides a reasonable amount of guidance with respect to the direction" "to practice a desired embodiment of the claimed invention" (see Remarks, top of page 7). Applicants' arguments have been fully considered but are not deemed persuasive for the reasons described below and reasons described in earlier Office Actions. Applicants further argue "the specification discloses a variety of

crystals" and "the fact that the inventor's chose only one of the crystals to move forward for further analysis, does not negate the existence of the other crystals." (see Remarks, middle of page 7). However, the instant specification describe only one crystal as shown in Table 9, page 24 with a X-ray diffraction-quality. "Applicants also point out that there is no need to test different conditions to obtain the optimal parameters in order to produce new crystals within the scope of the claim" (see Remarks, middle of page 7). However, this argument contradicts the statement by the instant specification reciting "crystallization was facilitated by the presence of ligands", i.e., further undue experimentation(s) would be required to make the IspA crystal without said ligands which is encompassed by the instant claims and using a crystallization conditions described in the instant application for one skilled in the art, for example.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The breadth of the claims: Claim 16 is so broad as to encompass any crystal having amino acid residues of 1-314 of SEQ ID NO: 1. Claims 1 and 4 are broad as to encompass any protein crystals or co-crystal with unit cell dimensions of +/- 5%, of a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{\circ}$, space group of P4122, and residues 1-314 of SEQ ID NO: 1 with optional additional limitations presented in individual, dependent claim form such as a certain resolution (Claim 4). Claims 6 is also so broad as to encompass any methods for forming a protein crystals or co-crystal with any ligand, having a unit cell dimensions of +/- 5%, of a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{\circ}$,space group of P4122, and residues 1-314 of SEQ ID NO: 1 with optional additional limitations presented in individual, dependent claim form such as a certain resolution (Claim 4).

The nature of the invention: The invention is related to a protein crystal of *E. coli* IspA and a method of crystallization thereof. At the time of the invention, methods of protein crystallization were well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the claimed crystals, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999, provided in the previous Office Action) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995, provided in the previous Office Action) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al.,

which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Along these same lines, Wiencek (*Ann Rev Biomed Eng* 1:505-534, provided in the previous Office Action) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other IspA, farnesyl pyrophosphate synthase, can be achieved using the crystallization parameters as set forth at p. 49 of the specification or in the presence of any ligand as encompassed by the claims. Alternatively, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of residues 1-314 of SEQ ID NO: 1 can be achieved using any crystallization parameters encompassed by the instant claims. Furthermore, the resolution "greater than 3.0 Angstroms" as disclosed in Claims 4 and 9 is not possible to predict by one skilled in the art because the resolution must be determined by X-ray crystallography.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only a single working example of the claimed crystal and the method of crystallization thereof. See specification at pp. 50, §00185. In Hosfield et al. (J.Biol.Chem. 279:8526-8529, provided in the previous Office Action), the

second *E. coli* IspA crystal with ligands IPP and DMASPP is known in the art within the scope of instant Claims. Other than these two working examples, the specification fails to provide guidance for altering the crystallization conditions for crystallizing proteins comprising residues 16-314 of SEQ ID No: 1 with an expectation of obtaining diffraction-quality crystals. Further, the specification fails to provide guidance for crystallizing residues 1-314 of SEQ ID NO: 1 (*E. coli* IspA protein) with any other ligands disclosed in the instant specification set forth at pp. 50 or any other conditions with an expectation of obtaining diffraction-quality crystals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these methods are specific to a particular protein with two combinations of ligands as evidenced by the above teachings. Thus, a skilled artisan is left to experiment by a trial and error process to determine whether the disclosed crystallization conditions can be applied to crystallization of other proteins or whether residues 16-314 of SEQ ID No: 1 can be crystallized under a different set of crystallization parameters.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Conclusion***

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
April 2, 2007

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER